Prospectus

Development of a Novel Cardiovascular Health Monitor
(Technical Topic)

A Look Into the Pitfalls and Future of U.S. Medical Device Regulation
(STS Topic)

By

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On my honor as a University student, I have neither given nor received unauthorized aid on this assignment as defined by the Honor Guidelines for Thesis-Related Assignments.

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Introduction

Cardiovascular disease (CVD) is the leading cause of death amongst both men and women, accounting for roughly one in every four deaths in the United States according to the CDC (Greenland, 1999; Fryar, 2012). Additionally, as of 2015, 41.5 percent of Americans had at least one CVD condition, with a projected increase to 45 percent by 2035 (Khavjou et al., 2016). Middle-aged people (35-55) are more at risk for CVD than young adults. Recently, however, the age group most at risk has been decreasing from the ages of 60 and above to the ages of 35 and older. Cardiovascular disease costs the US $318 billion per year in medical fees with an additional $237 billion coming from indirect costs such as loss of productivity. Cardiovascular disease risk factors can be classified as non-modifiable and modifiable, the former of which cannot be changed. These non-modifiable risk factors include, but are not limited to age, ethnicity, and genetics.

With a change in behavior, modifiable risk factors can be controlled or eliminated. The three key risk factors, smoking, high blood pressure, and high cholesterol are shared by 47% of Americans (Smith et al., 2004). Through daily physical exercise and by changing one's diet to exclude trans fats, saturated fats, and salts, one can reduce the risk of developing cardiovascular disease. Reduction of alcohol intake to no more than one and two drinks a day for females and males, respectively, has been shown to decrease high blood pressure (Fryar, 2012). Because cardiovascular disease affects a large number of people, it is imperative that biomedical engineers make an effort to mitigate it. Our team will therefore create a device which non-invasively assesses the blood vessel health and physical fitness of a patient in order to provide healthcare professionals with insight into their risk for CVD. Additionally, I will research the effects of the current regulatory process for medical devices on patients, inventors, and

healthcare professionals. My research will provide insight into what policy changes would create equal approval opportunities for new devices as well as improve the quality of life for end users of medical devices.

Technical Project: Measuring Pulse Wave Velocity

Pulse wave velocity (PWV) refers to the velocity of the pressure wave propagated through the aortic tree during the contraction of the left ventricle of the heart. PWV can be used as a measure of arterial stiffness, which can signal the onset of cardiovascular disease (Laurent, 2006; Zieman, 2005). Both age and cardiovascular disease can cause vessels to be stiffer, increasing the velocity of both the pressure wave and the reflected wave moving towards the heart after the systolic period. An increase in the reflected wave velocity creates more work for the cardiovascular system and can lead to complications (Laurent, 2006). The ability to quickly and accurately measure PWV has the potential to aid clinicians when clearing patients for surgery or other treatment by providing them with an objective measure of their cardiovascular health.

Currently, the methods used to measure pulse wave velocity are often costly, invasive, and time ineffective. These methods include threaded catheterization and echocardiography. Threaded catheterization is extremely invasive, requiring insertion of a catheter usually into the femoral artery. Hours of preparation and recovery time make this method inefficient for PWV measurement. Echocardiography data is gathered via doppler ultrasound or magnetic resonance imaging and sphygmomanometry, but is more expensive than catheterization and takes approximately 30 minutes to complete (Pereira, 2015). For this project, our team is creating a device using photoplethysmography (PPG), which emits red and infrared light into both the

earlobe and finger and records the absorbance of each light wavelength. Electrocardiography (ECG) is used to record the propagation of electrical signals in the heart at the same time that the PPG collects data (Liu, 2011). Our project uses a novel method of measuring PWV using PPG and ECG in tandem to calculate the pulse transit time (PTT). PTT is usually measured as the time between two pulse waves using PPG or the time between an R-wave on an ECG and a pulse wave generated by PPG (Webber, 2012). Our method takes into account the delay between return of the S-wave to its baseline.

Technical Project: Quantifying METS

Metabolic equivalents of task (MET) is a measurement of a person's energy expenditure as compared to their body mass. One MET is defined as the amount of oxygen consumed while a person is at rest. METs can provide an indication of a patient's cardiovascular health. For example, the task equivalent of 4 METs is the ability to climb one flight of stairs (van Remoortel, 2013). This measurement would be able to reduce the amount of time to determine a patient's preoperative clearance (Israel, 2007). METs could also be used to describe reduced exercise capacity, which is an early predictor of cardiac mortality and disease. Currently, METs are most often quantified subjectively by a healthcare professional asking a patient about their daily physical activity. Objective methods for calculating METs are time intensive and require specialized equipment that may be inconvenient for some patients, specifically the cardiopulmonary exercise test (CPET). CPETs are integrative tests involving walking on a treadmill or bicycling and measurement of oxygen exchange to quantify physical fitness (Balady et al, 2010). In addition to measuring PWV, our project will objectively quantify METS without the need for measurement of gas exchange.

Technical Project: Continuous Blood Pressure Monitoring

Blood pressure can be monitored either continuously or intermittently. Measuring arterial blood pressure continuously allows for better monitoring of hypertension and hypotension, however, the current method to do so is invasive, difficult to perform, and more time consuming that intermittent measurement by sphygmomanometer. Sphygmomanometry is prone to error. Improperly sized cuffs or improper positioning over the brachial artery can result in inaccurate measurements. PPG has been investigated in recent years as a non-invasive solution, but previous studies have failed to meet the International Standards Office , U.S. Association for the Advancement of Medical Instrumentation (AAMI), and European Society of Hypertension (ESH) accuracy standards (85% probability of achieving a tolerable error of $\leq$ 10 mmHg) for non-invasive measurement of blood pressure across the three main categories: hypertensive, normotensive, and hypotensive. Using these past investigations in conjunction with new research, we plan to create algorithms to measure blood pressure and meet these standards. The success of our investigation into the use of PPG as a viable option for the continuous measurement of blood pressure would result in a breakthrough in a field that has yet to provide an accurate solution, providing clinicians with valuable, real-time blood pressure data for their patients.

STS Research Project: The Pitfalls and Future of U.S. Medical Device Regulation

How does the regulation and approval of medical devices impact healthcare professionals, inventors, and patients, and how might it be improved? The subject of this research question by virtue of being a medical device relates to the vessel health monitor. All treatment and diagnostic equipment that is defined as a medical device in the United States, is subject to premarket

approval by the Federal Drug Administration (FDA). The approval process, while codified, is not strictly enforced upon new devices as opposed to drugs. In an essay on innovation in medical technology, Ariel Stern argued that the FDA approval process incentivized quicker approval times for pioneer drugs than for pioneer medical devices. Stern supported this claim by comparing the average pre-market approval time for "high-risk"-classified devices (18.1 months) against that of a device that is the first of its kind (22.5 months). In the same paper, the author used an empirical model of approval time based on Carpenter's 2010 model to illustrate the longer approval times for new devices (Stern, 2016).

The FDA approval process, most notably the 510(k) process, suffers from its inability to assess the safety of an approved device after it enters the market. Curfman and Redberg describe the Johnson & Johnson ASR XL Acetabular System hip implant, a modification of the earlier ASR Hip Resurfacing System. Because the ASR XL was a "substantially equivalent" device to an existing and approved device, it did not have to undergo clinical trials. The class III (high-risk) device was later recalled due to its reported 1 in 8 failure rate caused by erosion of metal particles which were free to enter the bloodstream, causing many patient deaths. By law, class III devices must undergo clinical trial and should not be approved by the 510(k), but often times high risk devices will slip through the cracks and skip trials.

The Institute of Medicine (IoM) in 2011 released a report on the 510(k) process and demonstrated its inability to ensure safety and recommended that the clearance type be eliminated. The IoM also recommended that approved devices be monitored throughout their market life cycle. This proposal was met with criticism and was not adopted by the FDA (Curfman & Redberg, 2012). In the recent past, others have made suggestions for the improvement of the approval process. Dhruva and Redberg argue in favor of postmarket

surveillance, citing the Sprint Fidelis defibrillator lead which was recalled after reports of patient deaths caused by the device in 2007. Because few studies existed which analyze the medical device approval process, the authors designed a study of their own. They found that 78% of approved devices were not considered high-risk. It was argued that this figure is alarming due to the number of devices that end up having to be recalled, further illustrating the need for a better post-market surveillance system. The authors declare that increased political funding and support is necessary for both the FDA and European Union in order to implement better programs. If funding is not made available for improved device assessment, the authors say, then data should be made available to the public (Dhruva & Redberg, 2012). Similarly, Feldman et al. wrote that inability to surveil products post-approval leaves the responsibility of failure reporting to academics, manufacturers, and end-users.

Additionally, the FDA is unable to regulate clinical procedure and healthcare professional use of approved devices, leading to potential off-label use which may harm patients. Professional societies, such as the American Heart Association, are often left to oversee the use of medical technologies in their domain, as well as provide best practices of their use. While they are not immune to bias and conflict of interests, the authors contend that they are useful vehicles of discussion and drive quality improvement (Feldman et al., 2007). My research will determine the best implementation of a new policy which optimizes patient health while allowing the greatest number of new devices in a timely manner comparable to that of previous devices.

Each of the key stakeholders described in the research question are heavily impacted by the regulation of medical devices. The societal context of medical devices can be described using the actor network theory (ANT) and technology-in-practice (TIP) frameworks. Prout (1996) proposes ANT as a means to discuss technology in terms of its contributions to peoples' health.

The approach is used to describe the role of the metered dose inhaler in the network. The technical portion of its role is its delegation of work as a stand-in for someone who must give a specific dosage of medicine. The authors describe the program of action (correct drug administration) as well as the user antiprogram (incorrect use of the device) of the device. The inhaler's network was considered to be the interaction between the engineers attempting to bring user action in line with the program (Prout, 1996).

Timmermans and Berg (2003) describe TIP as a mixture of social essentialism and technological determinism, in which technology is neither a deterministic super-actor that dehumanizes users nor is it a blank slate, but a combination of professionals, devices, patients, and records. The use of this framework allows for one to examine the health-benefiting goals that medical technologies allow people to accomplish by delegation of work (Timmermans & Berg, 2003). Using TIP, Gibson et al. were able to consider the cultural significance associated with a given technology that varies across different members of the network. The authors relate their interviews with men who use mechanical ventilators to aid their muscular dystrophy. From the interviews, the authors explore self-understanding of the body in conjunction with technology (i.e. where does the body end and the device begin?) (Gibson et al., 2007). Examining the sociotechnical dimensions of the technology using these frameworks will inform the creation of new policy.

Research Methods

In order to answer the question of how policy could be improved, I will be conducting a policy analysis, following Bardach's (2000) first four policy analysis steps. I first will gather background evidence to justify the need for policy reform by looking at the work of those who

create policies as well as those who are ultimately affected by them. I will identify potential options for new policies, examining medical device regulation policies from other nations. The nations chosen will be those with drastically different policies, including Japan, South Africa, and Canada. These will be compared with the current U.S. policy, compared to one another, and the most effective will be compiled and ranked. A broad range of alternatives will be compiled and then later narrowed down. Assessing these alternatives will involve considering who will be affected and how, the cost associated, and the sociopolitical history behind them (Policy Analysis). Finally, the policy best fitting the situation will be chosen. The best policy will insure the safety of end-users of medical devices, limit long approval times, and promote innovation in medical technology.

Timeline, Expected Outcomes, and Conclusion

Before the end of the calendar year, our team will have completed multiple working prototypes of the health monitor. Figure 1 is a Gantt chart detailing upcoming milestones and deadlines set by our team. By the end of January, we will complete our IRB-approved clinical trials of the device upon 40 patients, and a subset of ten patients will have their measurements taken using echocardiography (the current PWV measurement standard) for comparison. In the upcoming semester, we will iteratively improve upon the device as necessary, correcting algorithms to calculate METS and continuous blood pressure. I will conduct my policy analysis and determine the best fitting policy as described above. My literature review will be completed by the end of January. I plan to have compiled a list of policy alternatives by February. I anticipate that by the end of March, my STS research will result in a single policy able to be discussed in an academic review article along with the other potential options. The completion of

the health monitor will innovate the use of three major cardiovascular health indicators in clinic and provide physicians with more objective data from which to base their clinical decisions. My STS research will provide insight into how the U.S. medical device regulatory process can be improved.

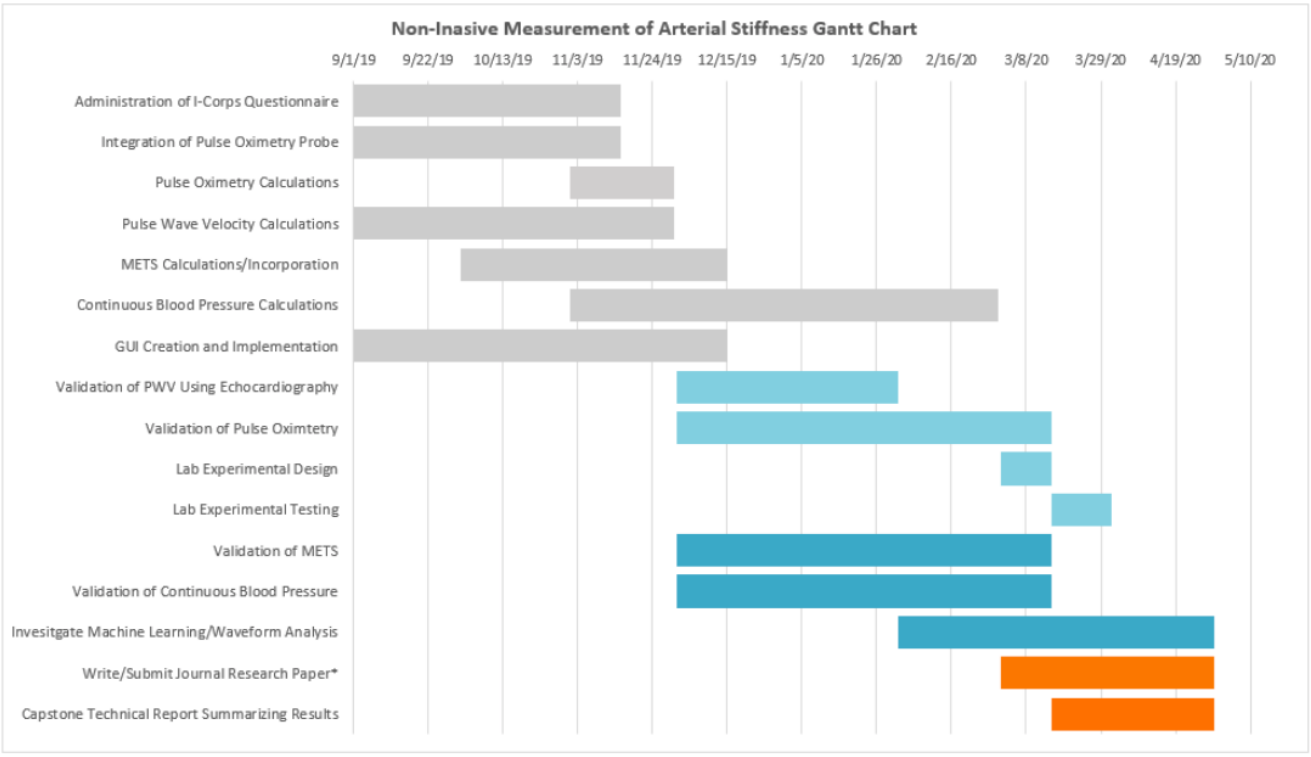

Figure 1. The Gantt Chart displays a list of milestones and deadlines for the vessel health monitor.

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